Claim 19, line 1 change "A method" to --The method--.

REMARKS

Reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.116, and in light of the remarks which follow, are respectfully requested. By the present amendments, Claims 1, 5, 16, 17, 18, and 19 have been amended substantially in accordance with the Examiners' suggestion. In particular, Claim 1 has been amended to functionally recite that the peptide administered comprises anti-inflammatory activity. Moreover, Claim 5 has been amended to correct the typographical error noted by the Examiner. Further, Claims 16-19 have been amended to change a method to the method in accordance with the Examiners' suggested change. Based on the foregoing, and the remarks which follow this application is believed to be in condition for allowance.

Claims 1-11 and 16-19 stand rejected under 35 U.S.C. §112, first paragraph, on the basis that they are broader than the enabling disclosure. This rejection is respectfully traversed for the same reasons set forth in Applicants Reply. Moreover, this rejection is believed to be moot because of the present amendment of Claim 1 to recite that the administered peptide comprises anti-inflammatory activity. It is noted, that the Examiner helpfully indicated in the response, that if the recited peptide were limited to those having anti-inflammatory func-

tions, then the rejection would be overcome. Therefore, based on the foregoing withdrawal of the §112, first paragraph, rejection of Claims 1-11 and 16-19 is respectfully requested.

Claims 1-3 stand rejected under 35 U.S.C. §102(b) as assertedly being anticipated by Ferreira et al. (U.S. Patent 5,389,615) or Oluyomi et al. (European Journal Pharmacology Volume 258 p. 131). This rejection is maintained for the reasons of record.

Based on the following, Applicants respectfully submit that the anticipatory rejection should be withdrawn. Essentially, as argued in Applicants' previous Reply, Ferreira et al teaches the use of the tripeptide K(d)PV for the treatment of pain. By contrast, the claimed method is directed to treatment of inflammation. As previously explained, pain cannot be equated to inflammation. Moreover, the mere indication that inflammation is sometimes associated with pain would not reasonably suggest that a peptide suitable for treatment of pain would necessarily be suitable for the treatment of inflammation. This is not withstanding in the fact that inflammation may be involved in some conditions, such as trauma or burns, which may involve inflammation. Also, the fact that the reference teaches that the subject peptide was known to antagonize hyperanalgesia would not reasonably suggest that such peptide would be capable of treating inflammation. Again, it would appear that the Examiner has equated inflammation and pain and analgesic activity to anti-

inflammatory activity. However, this is incorrect because these phenomenon are associated with completely different mechanisms.

Moreover, given these different mechanisms, compounds suitable for treatment of analgesia or exhibiting antipyretic effects do not necessarily possess anti-inflammatory activity. As evidence of this fact, Applicants attach to this Reply relevant pages from Chapter 12 of a book entitled "Drugs to Suppress Inflammatory and Immune Reactions". It should be noted that at page 282 the authors compare the analgesia, antipyretic and anti-inflammatory effects of various compounds. Specifically, this table compares the effects of Fenbufen, mefenamic acid and paracetamol. It should be noted that all these compounds possess analgesic and antipyretic effects. However, they possess no anti-inflammatory activity. Moreover, the same reference teaches that paracetamol possesses an analgesic and antipyretic effects but no anti-inflammatory activity. Therefore, this substantiates Applicants previous argument that it cannot be extrapolated that a compound suitable for treatment of analgesia or pain would have any activity for inhibiting inflammation. Essentially, it is impossible to predict with any level of certainty that a compound possessing analgesic or antipyretic effects would necessarily possess anti-inflammatory activity.

Turning now to Oluyomi, this reference similarly teaches the anti-nociceptive (anti-pain) effect of different compounds. As with Ferreira et al, this reference similarly does not teach

or suggest that the disclosed peptide could be used for treatment of inflammation. Moreover, for the reasons set forth above, it is not proper to assume absent any evidence that a compound capable of inhibiting pain would be capable of inhibiting inflammation. As discussed above, while inflammation may be associated with pain, compounds which inhibit pain do not necessarily inhibit inflammation. To the contrary, pain and inflammation are caused by different mechanisms, and are not necessarily inhibited by the same compounds. Essentially, Oluyomi concludes that the compounds studied possess good analgesic activity. However, he does not conclude that they could be used to inhibit inflammation as claimed.

In fact, the reference would suggest the contrary. It should be noted that Oluyomi states at page 137, lines 31-36, that it had been previously reported by Hiltz (*Peptides*, Volume 12, pages 767-771) that this compound has no effects on inflammation. This reference was previously made of record during prosecution of this application. The Examiner is respectfully directed to the abstract wherein the reference indicates that this peptide exhibited no inflammatory activity. In fact, the reference indicates that the results suggest that the L-pro amino acid is <u>essential</u> for the anti-inflammatory activity (which is not comprised in the peptides used in the claimed invention). Therefore, evidence is of record which would have reasonably suggested that the recited peptides would not possess

activity as an anti-inflammatory agent. Quite surprisingly, the present inventors have discovered that a peptide containing the lysine-proline-valine tripeptide, in which the proline residue is in its dextrorotatory optical isomer form, possesses anti-inflammatory activity. Therefore, the results of the invention are unexpected. Based on the foregoing, Applicants respectfully request that the §102(b) rejection of Claims 1-3 based on Ferreira et al or Oluyomi et al be withdrawn as these references, alone or in combination, do not teach or suggest the anti-inflammatory activity of the recited peptide. To the contrary, the Oluyomi et al reference would suggest that such peptide would not possess any activity as an anti-inflammatory agent.

Claims 4, 7-10 and 18 stand rejected under 35 U.S.C. §103 as being unpatentable over Ferriera et al, taken as applied to Claims 1-3 above. This rejection is respectfully traversed for the same reasons as the §102 rejection based on this reference. Essentially, the prior art would not reasonably suggest the anti-inflammatory activity of the subject peptides. To the contrary, for the reasons set forth above, compounds which exhibit activity as analgesics or antipyretics do not necessarily possess activity as anti-inflammatory agents. As discussed above, these biological phenomenon are caused by different mechanisms, and therefore often must be treated using different compounds. This is substantiated by the reference attached to

this Reply, which compares the analgesic, antipyretic and anti-inflammatory activity of various compounds. It can be clearly seen that compounds which possess good analgesic and antipyretic effects may exhibit no anti-inflammatory activity. Therefore, the cited reference would not reasonably suggest the claimed invention.

Moreover, the rejection should further be withdrawn based on the unexpected results achieved by the claimed invention. Based on the information disclosed in Oluyomi et al, discussed above, and Hiltz cited therein, the reasonable expectation prior to the present invention would have been that the subject peptides would exhibit no ability to inhibit inflammation. Quite surprisingly, the present inventors discovered that, in fact, the subject peptides effectively inhibit inflammation. Therefore, based on these results, which are not suggested by the prior art, withdrawal of the §103 rejection based on Ferreira et al is respectfully requested.

Claims 5-6 and 19 stand rejected under 35 U.S.C. §103 as being unpatentable over Ferreira et al, taken in view of Lipton and Oluyomi. Essentially, for the reasons set forth above, Ferreira et al does not teach or suggest the claimed invention. Essentially, it cannot be reasonably extrapolated that compounds suitable for treatment of analgesia or pyrexia would have any ability to inhibit inflammation. This is further substantiated by the reference attached to this Reply. Moreover, as for the

reasons previously argued, Lipton and Oluyomi do not cure the deficiencies of the primary reference. To the contrary, Oluyomi et al would reasonably suggest that the subject peptides would be incapable of inhibiting inflammation. In this regard, the Examiner is again respectfully referred to the disclosure of page 137, lines 31-36, and the Hiltz reference previously provided to the Examiner. This reference teaches that the L-P(d)-V peptide has no effects on inflammation. The Examiner is respectfully referred to the Hiltz abstract wherein they teach the essential nature of the L-Pro form of the amino acid which is purportedly essential for anti-inflammatory activity. Therefore, this reference would have suggested that the subject peptides would be incapable of inhibiting inflammation. Lipton was cited based on its disclosure relating to the use of protected peptides in favor of non-protected peptides in order to enhance stability. The use of protected forms of peptides for enhanced stability is acknowledged to have been known prior to the present invention. However, this does not cure the deficiencies of Ferreira or Oluyomi, for the reasons set forth above. Therefore, withdrawal of the §103 rejection based on Ferreira taken in view of Lipton and Oluyomi is respectfully requested.

Claims 1-11, 16 and 19 stand rejected under 35 U.S.C. §103 as being unpatentable over Ferreira in view of Nordlund, Lipton and Remington's Pharmaceutical Sciences and Oluyomi. This

rejection is respectfully traversed for the same reasons set forth above. Essentially, Ferreira and Oluyomi do not reasonably suggest the anti-inflammatory activity of the subject peptides. To the contrary, Ferreira is limited to the use of the subject peptides for treatment of pain, i.e., analgesia. However, the reference does not indicate that such peptides would have any effect on inflammation. Moreover, the fact that compounds suitable for treatment of analgesia do not necessarily inhibit inflammation is substantiated by the reference attached to this Reply. In fact, Oluyomi et al, actually teaches against the claimed invention. Again, the Examiner is respectfully referred to the disclosure at page 137, lines 31-36, and the Hiltz reference submitted during prosecution. The secondary reference, i.e., Lipton, is again cited for its disclosure relating to stable protected peptides. As noted above, this is acknowledged to have been known prior to the present invention. However, this reference similarly does not teach the use of the subject peptides as anti-inflammatory agents.

Remington's is again cited based on its disclosure of various topical formulations and use thereof for administration of active agents. This also is acknowledged to have been known prior to the present invention. However, this does not cure the deficiencies of the rejection. Therefore, based on the failure of any of the references to teach or suggest the anti-inflamma-

tory activity of the subject peptides, the rejection should be withdrawn.

Further, Claims 1-3, 5-11 and 16-19 stand rejected under 35 U.S.C. §103 as being unpatentable over Oluyomi et al, taken in view of Nordlund, Lipton and Remington's Pharmaceutical Sciences. This rejection is respectfully traversed for the same reasons set forth above. Essentially, for the reasons set forth above, Oluyomi et al fails to teach or suggest the use of the subject peptides for treatment of inflammation. To the contrary, this reference actually teaches against the claimed invention. As discussed above, this reference specifically refers to previous reports which had indicated that the subject peptides cannot be used to inhibit inflammation. This is substantiated based on the disclosure at page 131, lines 137, lines 31-36, and Hiltz (*Id.*) discussed above. The secondary references do not cure the deficiencies of Oluyomi. These references are relied upon for their disclosure relating to the use of protected peptides, and for preparation of topical formulations including those containing peptides. Topical formulations containing peptides for pharmaceutical use is acknowledged to have been known prior to the present invention. However, again none of the references would teach or suggest the topical administration of the subject peptides for inhibition of inflammation. To the contrary, the primary reference would suggest that such a method would be inefficacious. Therefore, withdrawal of

the §103 rejection based on Oluyomi et al, taken in view of Nordlund, Lipton and Remington's Pharmaceutical Sciences, is respectfully requested.

Finally, Claims 5-6 and 16-19 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner has noted various informalities in Claim 5 and 16-19. By the present Amendment, all of the Examiner's suggested changes have been made. Therefore, withdrawal of the §112, second paragraph, rejection of Claims 5-6 and 16-19 is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Reply the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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